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(54) [Title of the Invention] LIPASE INHIBITORY SUBSTANCE DERIVED FROM HOP

(57) [Abstract]

[Problem to be Solved]

To provide a food or a medicinal composition having effects of suppressing digestion and absorption of lipid, requiring no dietary restriction, derived from natural products, highly safe, and having an antiobestic activity, and, in further detail, to provide polyphenols derived from a hop or a hop bract as a lipase inhibitor or a lipase inhibiting food.

[Solution]

A lipase inhibitory substance that is a polyphenol substance contained in a hop and is characterized by having a property of being adsorbed to a gel-type synthetic resin, and a food and drink containing the lipase inhibitory substance.

[Claims for the Patent]

[Claim 1]

A lipase inhibitory substance being a polyphenol substance contained in a hop, characterized by having a property of being adsorbed to a gel-type synthetic resin.

[Claim 2]

A lipase inhibitory substance being a polyphenol substance contained in a hop, characterized in that the substance does not pass through an ultrafiltration membrane having a molecular weight cut-off of 1000 or more in the treatment with the membrane.

[Claim 3]

A lipase inhibitory substance being a polyphenol substance contained in a hop, characterized in that the substance has a property of being adsorbed to a gel-type synthetic resin and does not pass through an ultrafiltration membrane having a molecular weight cut-off of 1000 or more in the treatment with the membrane.

[Claim 4]

The lipase inhibitory substance according to any one of claims 1 to 3, wherein the hop is a hop bract.

[Claim 5]

A lipase inhibitor, characterized by containing an effective amount of a lipase inhibitory substance according to any one of claims 1 to 4.

[Claim 6]

A food and drink, characterized by containing a lipase inhibitory substance according to any one of claims 1 to 4.

[Detailed Description of the Invention]

[0001]

[Field of the Invention]

The present invention relates to a lipase inhibitory substance derived from a hop and application thereof.

[0002]

[Conventional Art]

Hop plants are perennial plants of the family Moraceae, and the cone thereof (matured unfertilized female flower) is generally called a hop. The lupulin part (yellow granules formed on the root of internal bract in the cone) of the hop causes bitterness and flavoring of the hop and is an important material for beer brewing, as well as yeast and malt. The hop is also used as a tranquilizer or an anti-aphrodisiac agent in a folk medicine.

[0003]

The hop bract is a hop cone of which the lupulin part is removed and is useless for beer brewing and, in some cases, is eliminated in beer brewing. The useless hop bract is used as a fertilizer for soil improvement, but no other specific effective usage has been found. Accordingly, usage with a higher added value has been desired to be developed. The same is applied to a hop plant body such as leaves and stems.

[0004]

Japanese Patent Laid-Open Nos. 9-2917, 9-163969, 9-295944, and 10-25232 describe that polyphenols derived from a hop, in particular, from a hop bract have an antioxidative activity, a

foam-stabilizing activity against foaming malt beverages, an anti-caries activity, and a deodorant activity.

[0005]

Recently, in Japan, obesity on account of westernized dietary habits and chronic insufficient exercise is a significant problem as a risk factor of lifestyle-related diseases such as hypertension, heart diseases, and diabetes mellitus. At present, these lifestyle-related diseases account for about 60% of causes of death of the Japanese and are thought to be treated or prevented by preventing obesity. Inhibitors for digestive enzymes such as lipase are known as therapeutic agents of obesity caused by intake of excessive nutrition. Lipase is an enzyme decomposing lipids, and it is thought that obesity can be prevented and cured by inhibiting lipase to suppress absorption of lipid in foods.

[0006]

As polyphenols having a lipase-inhibiting activity, tannins contained in feed plants (British J. Nutrition, (1988), 60, 275), tannins, flavonoids, and glycosides thereof contained in Cassia minosoides subsp. nomame, which is a fabaceous plant (Japanese Patent Laid-Open Nos. 8-259557 and 7-61927), and triterpene compounds and derivatives thereof (Japanese Patent Laid-Open No. 9-40689) are confirmed.

[0007]

Furthermore, a lipase inhibitor including a water extract of sweet pepper, pumpkin, Lyophyllum shimeji, Grifola frondosa, Hizikia fusiformis, green tea, black tea, or oolong tea (Japanese Patent Laid-Open No. 3-219872), a lipid absorption-

inhibiting food blended with epigallocatechin gallate, which is the main component in green tea (Japanese Patent Laid-Open No. 3-228664), and an antiobestic agent containing procyanidin as an active ingredient (Japanese Patent Laid-Open No. 9-291039) are disclosed.

[0008]

As described above, many substances having an activity of inhibiting lipase have been reported, but every substance is insufficient in effect and safety aspects.

[0009]

[Problems to be Solved by the Invention]

The object of the present invention is to provide a food or medicinal composition having effects of suppressing digestion and absorption of lipid, requiring no dietary restriction, derived from natural products to be highly safe, and having an antiobestic activity, and, in further detail, to provide polyphenols derived from a hop or a hop bract as a lipase inhibitor or a lipase inhibiting food.

[0010]

[Means for Solving the Problems]

The present inventors have conducted intensive studies on the above-mentioned problems, and as a result, have found that a substance that is a polyphenol substance contained in a hop, in particular, in a hop bract, has a property of being adsorbed to a gel-type synthetic resin and does not pass through an ultrafiltration membrane having a molecular weight cut-off of 1000 or more in the treatment with the membrane can be used as a lipase inhibitor. That is, a hop, in particular, a hop bract is

extracted with water or an aqueous solution of a water-miscible organic solvent, and the extract is treated with a gel-type synthetic resin or an ultrafiltration membrane. The fraction obtained by the above treatment processes is a substance that can be used as a lipase inhibitor. Furthermore, the present invention has been accomplished by utilizing this substance in a drug or a food and drink.

[0011]

A first aspect of the present invention relates to a lipase inhibitory substance being a polyphenol substance contained in a hop, characterized by having a property of being adsorbed to a gel-type synthetic resin.

[0012]

A second aspect of the present invention relates to a lipase inhibitory substance being a polyphenol substance contained in a hop, characterized in that the substance does not pass through an ultrafiltration membrane having a molecular weight cut-off of 1000 or more in the treatment with the membrane.

[0013]

A third aspect of the present invention relates to a lipase inhibitory substance being a polyphenol substance contained in a hop, characterized in that the substance has a property of being adsorbed to a gel-type synthetic resin and does not pass through an ultrafiltration membrane having a molecular weight cut-off of 1000 or more in the treatment with the membrane.

[0014]

A fourth aspect of the present invention relates to the lipase inhibitory substance according to any one of the above claims 1 to 3, wherein the hop is a hop bract.

[0015]

A fifth aspect of the present invention relates to a lipase inhibitor characterized by containing an effective amount of the lipase inhibitory substance according to any one of the above claims 1 to 4.

[0016]

A sixth aspect of the present invention relates to a food and drink characterized by containing the lipase inhibitory substance according to any one of the above claims 1 to 4.

[0017]

[Embodiments of the Invention]

The hop bract used as a raw material in the present invention is obtained by removing the lupulin part from a hop cone. In general, the hop cone is pulverized, and then the lupulin part is removed by filtration to give a hop bract. However, recent beer brewing has a tendency that the hop cone, which is useless for bear brewing, is formed into a pellet form without being removed and is used in beer brewing as a hop pellet, in order to save the trouble of removing the hop bract by filtration. Therefore, any hop containing a hop bract can be used as a raw material of the present invention without particular limitation, and a hop cone containing a hop bract and a hop pellet can be used as a raw material without any problem.

[0018]

In a method manufacturing the lipase inhibitory substance, a raw material of a hop bract, a hop cone containing a hop bract, a hop pellet, or the like is extracted with water or an aqueous solution containing 50 v/v% or less of a water-miscible solvent such as alcohol, acetone, or acetonitrile. A preferable example is water or a water-containing ethanol containing 50 v/v% or less of ethanol. The ratio of a raw material and an extraction solvent is preferably about 1:20 to 1:100 (weight ratio). The extraction is preferably conducted at 4 to 95°C for about 20 to 60 minutes with stirring. This crude extract liquid is filtered to give an extract liquid. On this occasion, a filter aid such as perlite may be used, if necessary. The thus obtained extract liquid is treated with a gel-type synthetic resin and/or an ultrafiltration membrane.

[0019]

(Use of gel-type synthetic resin) First, a method using a gel-type synthetic resin will be described. A lipase inhibitory substance is obtained by an adsorption process of adsorbing the lipase inhibitory substance to a gel-type synthetic resin by applying the extract liquid obtained by the aforementioned extraction process, a washing process of washing the gel-type synthetic resin with water or an organic solvent, preferably an ethanol aqueous solution, and particularly preferably 1 to 10 v/v% of ethanol aqueous solution, and an elution process of eluting the lipase inhibitory substance from the gel-type synthetic resin with an organic solvent, preferably a 60 v/v% or more of ethanol aqueous solution or ethanol.

[0020]

In the adsorption process, the extract liquid is cooled to about room temperature of 15 to 30°C and then applied to a column packed with the gel-type synthetic resin to adsorb the lipase inhibitory substance to the resin. In the process, if necessary, the organic solvent concentration in the extract liquid may be previously decreased by concentration under reduced pressure in order to increase adsorption efficiency, if necessary. Examples of the material for the gel-type synthetic resin include hydrophilic vinyl polymers, hydroxypropylated dextran, and styrene-divinylbenzene copolymers. There are various gel-type synthetic resins as described on pages 30 to 31 and 123 to 131 of "DIAION I basic edition", published by Mitsubishi Chemical Corp. on January 10, 1995 (Heisei 7) as synthetic adsorbents, for example. Since adsorbing ability to polyphenol varies depending on the type of the respective resin, it is desired to select a resin according to the purpose. In the present invention, any resin that can give a predetermined molecular weight fraction can be used. The time for liquid application is preferably determined so that the SV value is in the range of 0.5 to 100. Here, the SV value is defined by the following equation:

[Expression 1] SV value = [liquid application amount (L)]/{[resin amount (L)] × [application time (h)]}.

[0021]

In the aforementioned washing process, the gel-type synthetic resin holding the lipase inhibitory substance is washed. With this process, impurity components are removed to increase the purification degree of the lipase inhibitory

substance. The solvent used for the washing is preferably water or a 1 to 10 v/v% ethanol aqueous solution, and a solvent amount of 1 to 10 times that of the resin is desirably used for the washing.

[0022]

In the aforementioned elution process, the lipase inhibitory substance is desorbed and eluted from the gel-type synthetic resin holding the lipase inhibitory substance. The solvent used for the elution may be water-containing alcohol, water-containing acetone, water-containing acetonitrile, or the like, and a 30 v/v% or more of ethanol aqueous solution and ethanol are particularly preferred. The amount of an elution solvent to be applied is desirably about 2 to 6 times that of the resin.

[0023]

The resulting elution solvent is removed by a usual method such as concentration, lyophilization, or spray drying to give a powder of the lipase inhibitory substance. In concentration under reduced pressure, alcohol, acetone, acetonitrile, or the like may be recovered for reusing it. The gel-type synthetic resin used can be used repeatedly by washing with an 80 v/v% or more of alcohol aqueous solution, an about 0.05 N of sodium hydroxide aqueous solution, or the like.

[0024]

(Use of ultrafiltration membrane) Next, a method using an ultrafiltration membrane will be described. The hop extract liquid obtained by the aforementioned extraction process is treated with an ultrafiltration membrane having a molecular weight cut-off of 1000 or more. In the process, if necessary,

the organic solvent concentration may be decreased by concentrating the extract liquid under reduced pressure. The recovered organic solvent may be reused. Any material that is usually used as an ultrafiltration membrane can be used without any particular limitation, and examples thereof include cellulose, cellulose acetate, polysulfone, polypropylene, polyester, polyethersulfone, and PVDF. Furthermore, any membrane that has a molecular weight cut-off is 1000 or more can be used without particular problems. However, if the molecular weight cut-off is too large, the yield is significantly decreased. If the molecular weight cut-off is small, the treatment takes a long time. Accordingly, an ultrafiltration membrane having a molecular weight cut-off of 10000 to 50000 is preferable. In addition, the treatment is determined depending on the type of an extraction solvent and the ratio of an extraction solvent and a hop or a hop bract and is preferably conducted until the amount of a liquid remaining on the membrane becomes about one-tenth to one-hundredth that of the start of the treatment. The pressure in the treatment is determined depending on an ultrafiltration membrane and an ultrafilter and is preferably about 0.1 to 10.0 kg/cm^2. Furthermore, if necessary, the liquid treated once and remaining on the membrane may be diluted again with a proper solvent such as water and may be similarly retreated to increase the purification degree.

[0025]

The solvent of the liquid remaining on the membrane is removed by a usual method such as concentration, lyophilization, or spray drying to give a powder of the lipase inhibitory

substance. In concentration under reduced pressure, alcohol, acetone, acetonitrile, or the like may be recovered for reusing it.

[0026]

The thus obtained lipase inhibitory substance is an odorless flesh-colored, brown, or light-yellow powder with a slight bitterness and is a polyphenol substance that is adsorbed to a gel-type synthetic resin and does not pass through an ultrafiltration membrane having a molecular weight cut-off of 1000 or more in the treatment with the membrane. Furthermore, the yield is 0.5 to 20.0 w/w% when converted to a hop bract weight and 0.5 to 15.0 w/w% when converted to a hop cone weight.

[0027]

Since the active ingredients of the lipase inhibitory substances obtained by the method using a gel-type synthetic resin and the method using an ultrafiltration membrane are identical polyphenols, the purification degree of the polyphenols, which are an active ingredient, can be further increased by dissolving the lipase inhibitory substance obtained by the method using a gel-type synthetic resin in a proper solvent such as an alcohol aqueous solution and applying the solution to an ultrafiltration membrane. In addition, treatment in reversed order is possible. Obviously, a sufficiently useful lipase inhibitory substance can be obtained by the method using a gel-type synthetic resin or the method using an ultrafiltration membrane alone.

[0028]

The obtained lipase inhibitory substance can be made into a drug with a carrier, an aid, an additive, and the like that are generally used, can be used as a medicine by preparing an oral administration product according to a general method, or can be made into a food and drink by mixing with a food material.
[0029]

The medicine may be formulated as a tablet, a capsule, granules, syrup, or the like for oral administration. When these products are administered into human body as a medicine, a dose of 125 to 2000 mg/kg (body weight) and preferably 250 to 1000 mg/kg (body weight) per time is administered once or several times per day to sufficiently exhibit the effects.
[0030]

The medicine containing the lipase inhibitory substance of the present invention can have a unit volume form required together with physiologically acceptable vehicle, carrier, excipient, integrating agent, stabilizer, flavoring, and the like. Examples of reagents mixed in the tablet or capsule include binders such as tragacanth, gum arabic, cornstarch, gelatin; excipients such as crystalline cellulose; bulking agents such as cornstarch, completely gelatinized starch, and alginic acid; lubricants such as magnesium stearate; sweeteners such as sucrose, lactose, and saccharin; and flavorings such as peppermint, akamono oil, and cherry. In addition, a capsule formulation may further contain other liquid carriers such as oils in addition to the previous materials. Furthermore, other materials may be used as a coating agent. Furthermore, the physical form of a drug can be modified by another method. For

example, a tablet can be coated with shellac and sugar. Syrup or an elixir agent can contain sucrose as a sweetener, methyl or propylparaben as a preservative, a pigment, and flavoring such as a cherry or orange flavor.

[0031]

The food and drink containing the lipase inhibitory substance of the present invention may be in the aforementioned formulation or may be in a form of candy, a rice cracker, a cookie, or drink by adding a required amount of the lipase inhibitory substance to the respective food materials and processing by a usual manufacturing method. A health food or a functional food is ingested for preventing diseases and maintaining health. Therefore, 6.25 to 100 g/day, preferably, 12.5 to 50 g/day of a processed food is orally ingested severally divided.

[0032]

When the lipase inhibitory substance is added to these foods and drinks, a powder of the lipase inhibitory substance may be directly added to each of the foods and drinks, but preferably an aqueous solution, an alcohol aqueous solution, or an alcohol solution containing 1 to 2 wt% of a lipase inhibitory substance is prepared, and this solution is added to a food and drink so that the final concentration is 0.001 to 15 wt% and preferably 0.01 to 10 wt%. The drug and the food and drink containing the lipase inhibitory substance of the present invention has an effect suppressing absorption of lipid and therefore effective for prevention and treatment of obesity.

[0033]

[Examples]

Examples will now be described, but the present invention is not limited thereto.

[0034]

Example 1 (Preparation of lipase inhibitory substance from hop cone with gel-type synthetic resin)

Twenty grams of hop cones were pulverized in a mortar and extracted with 2 L of water under stirring at 95°C for 40 minutes. After filtration, the extract liquid was allowed to cool and then applied to a column packed with 80 mL of a hydrophilic vinyl polymer resin (Toyopearl HW40, Tosoh) over 2 hours (SV = 12.5). Then, the column was washed with 400 mL of a 5% ethanol aqueous solution. Furthermore, 400 mL of an 80% ethanol aqueous solution was applied to the column, and the eluate was collected and lyophilized to give 800 mg of a lipase inhibitory substance as an odorless light-yellow powder with a slight bitterness. The yield from the hop cone was 4%.

[0035]

Example 2 (Preparation of lipase inhibitory substance from hop bract with gel-type synthetic resin)

Twenty grams of hop bracts were extracted with 600 mL of a 50% ethanol aqueous solution under stirring at 80°C for 40 minutes. After filtration, the extract liquid was concentrated under reduced pressure to a volume 300 mL. The concentrated liquid was applied to a column packed with 80 mL of a styrene-divinylbenzene resin (Sepabeads 825, Mitsubishi Chemical) over 1 hour (SV = 3.75). Then, the column was washed with 400 mL of

water. Furthermore, 400 mL of an 80% ethanol aqueous solution was applied to the column, and the eluate was collected and lyophilized to give 1.6 g of a lipase inhibitory substance as an odorless light-yellow powder with a slight bitterness. The yield from the hop bract was 8%.

[0036]

Example 3 (Preparation of lipase inhibitory substance from hop cone with ultrafiltration membrane)

Twenty grams of hop cones were pulverized in a mortar and extracted with 2 L of water under stirring at 95°C for 40 minutes. After filtration, the extract liquid was allowed to cool and then treated with an ultrafiltration membrane having a molecular weight cut-off of 50000 (XM50, Amicon) at 1.0 kg/cm^2 at room temperature until the volume was reduced to 20 mL. The liquid remaining on the membrane was dried under reduced pressure to give 200 mg of a lipase inhibitory substance as an odorless light-yellow powder with a slight bitterness. The yield from the hop cone was 1%.

[0037]

Example 4 (Preparation of lipase inhibitory substance from hop bract with ultrafiltration membrane)

Twenty grams of hop bracts were extracted with 600 mL of a 50% ethanol aqueous solution under stirring at 80°C for 40 minutes. After filtration, the extract liquid was treated with an ultrafiltration membrane having a molecular weight cut-off of 10000 (YM10, Amicon) at 3.0 kg/cm^2 at room temperature until the volume was reduced to 60 mL. The liquid remaining on the membrane was lyophilized to give 0.8 g of a lipase inhibitory

substance as an odorless light-yellow powder with a slight bitterness. The yield from the hop bract was 4%.

[0038]

Example 5 (Further purification and qualitative analysis of lipase inhibitory substance)

The lipase inhibitory substance (0.8 g) prepared in Example 2 was dissolved in 500 mL of a 10% ethanol aqueous solution, and the resulting solution was treated with an ultrafiltration membrane having a molecular weight cut-off of 10000 (YM10, Amicon) at 1.0 kg/cm^2 at room temperature until the volume was reduced to 20 mL. The liquid remaining on the membrane was lyophilized to give 0.4 g of a lipase inhibitory substance as an odorless flesh-colored powder with a slight bitterness. Three grams of this powder was dissolved in 100 mL of methanol. The resulting solution was subjected to UV absorption spectroscopy analysis to give a characteristic spectrum having an absorption maximum at 280 nm and an absorption minimum at 260 nm, as shown in Figure 1. In addition, quantitative analysis of catechin (official food analysis), which is one of general quantitative analysis methods of polyphenols, gave a value of 40.6% when converted to a catechin content.

[0039]

Example 6 (tablet, capsule)

Substance prepared in Example 5	10.0 g
Lactose	75.0 g
Magnesium stearate	15.0 g
Total	100.0 g

The above components were uniformly mixed and formed to tablets and capsules according to usual methods. In addition, tablets and capsules were similarly formed using the same amount of each substance prepared in Examples 1 to 4 instead of the substance prepared in Example 5.

[0040]

Example 7 (powder, granules)

Substance prepared in Example 5	20.0 g
Starch	30.0 g
Lactose	50.0 g
Total	100.0 g

The above components were uniformly mixed and formed to powder and granules according to usual methods. In addition, powders and granules were similarly formed using the same amount of each substance prepared in Examples 1 to 4 instead of the substance prepared in Example 5.

[0041]

Example 8 (candy)

Sucrose	20.0 g
Starch syrup (solid content: 75%)	70.0 g
Water	9.5 g
Coloring	0.45 g
Flavoring	0.045 g
Substance prepared in Example 5	0.005 g
Total	100.0 g

The above components were formed to candy according to a usual method. In addition, candy was similarly formed using the same amount of each substance prepared in Examples 1 to 4 instead of the substance prepared in Example 5.

[0042]

Example 9 (juice)

Concentrate of orange juice	15.0 g
Fructose	5.0 g
Citric acid	0.2 g
Flavoring	0.1 g
Coloring	0.15 g
Sodium ascorbate	0.048 g
Substance prepared in Example 5	0.002 g
Water	79.5 g
Total	100.0 g

The above components were formed to juice according to a usual method. In addition, juice was similarly formed using the same amount of each substance prepared in Examples 1 to 4 instead of the substance prepared in Example 5.

[0043]

Example 10 (cookie)

Weak flour	32.0 g
Whole egg	16.0 g
Butter	16.0 g
Sugar	25.0 g
Water	10.8 g
Baking powder	0.198 g
Substance prepared in Example 5	0.002 g
Total	100.0 g

The above components were formed to cookie according to a usual method. In addition, cookie was similarly formed using the same amount of each substance prepared in Examples 1 to 4 instead of the substance prepared in Example 5.

[0044]

Example 11 (Effect of inhibiting lipase)

The measurement of lipase activity was conducted by using an oleic acid ester of 4-methylumbelliferone (4-MUO) as a substrate and porcine pancreatic lipase as an enzyme and measuring the fluorescence intensity of the produced 4-methylumbelliferone (4-MU). A hundred microliters of a McIlvaine buffer solution (pH 7.4) suspending 0.1 mM of 4-MUO, 100 μL of a McIlvaine buffer solution containing 4.5 μg of porcine pancreatic lipase dissolved therein, and 5 μL of a test solution were mixed and subjected to a reaction at 37°C for 20 minutes. Then, the reaction was terminated by adding 1 mL of 0.1 N hydrochloric acid, and the pH was adjusted to about 4.3 by adding 2 mL of 0.1 M sodium citrate. The fluorescence intensity of 4-MU produced by the reaction was measured at excitation wavelength 320 nm and emission wavelength 450 nm using a fluorometer. As the test sample for activity measurement, the substance obtained in Example 5 was used. In addition, epicatechin gallate, which is one type of polyphenol contained in teas at a large amount, was measured for the activity as a comparative sample. The inhibition activity of each sample is shown by an amount (IC50 value) of the sample necessary for reducing the activity of a control that does not contain the samples by a half. The results are shown in Table 1 and confirmed that the substance prepared in Example 5 had an inhibition activity higher than that of epicatechin gallate.

[0045]

[Table 1]

Enzyme-inhibiting activity (IC50 value)

	Inhibition activity (μg/mL)
epicatechin gallate	118
substance prepared in Example 5	1.18

[0046]

[Advantages of the Invention]

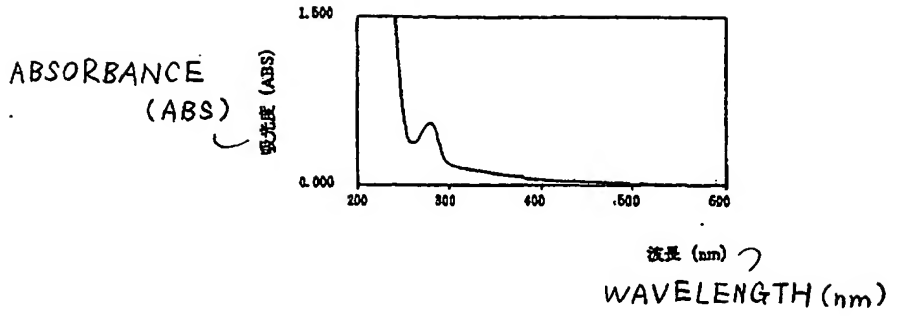
According to the present invention, a lipase inhibitory substance can be prepared by using a hop, such as a hop bract and a hop cone containing a hop bract, as a raw material. Furthermore, this substance can be readily utilized as a material for a drug or a food and drink.

[Brief Description of the Drawing]

[Figure 1]

Figure 1 shows a UV absorption spectrum of the substance prepared in Example 5, and the vertical axis indicates absorbance and the horizontal axis indicates wavelength (nm).

【図1】



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LL01 LL03 LL09
4B018 LB01 LB08 LE01 LE02 LE03
MD48 ME01 MF02
4B032 DB21 DG02 DK12 DK36 DK45
DK47
4C088 AB34 AC03 BA19 BA22 CA05
CA08 CA13 CA17 NA14 ZC20
ZC33

Figure 1

#1 ABSORBANCE (ABS)

#2 WAVELENGTH (nm)